Lactic Acidosis, Hypoglycemia, and Eosinophilia

Halle-Smith, James M; Hann, Angus; Cain, Owen L; Perera, M Thamara P R; Neil, Desley A H

DOI:
10.1002/lt.26101

Lactic Acidosis, Hypoglycemia, and Eosinophilia: Novel Markers of Antibody-Mediated Rejection Causing Graft Ischemia

TO THE EDITOR:

Historically, minimal significance has been given to the humoral immune response after liver transplantation and despite antibodies against human leukocyte antigens (HLAs) being present in 10% to 20% of patients awaiting transplant, the incidence of antibody-mediated rejection (AMR) after ABO compatible (ABO-C) liver transplantation is low.[1] Donor-specific antibodies (DSAs) can lead to early graft loss,[2] but most patients awaiting liver transplantation are not screened for HLA sensitization, and serum DSA measurement is only undertaken if AMR is suspected. We describe 2 cases of AMR occurring within 1 week of ABO-C liver transplantation with previously unreported biochemical and histological characteristics.

The first case was a 23-year-old woman who received a transplant for congenital hepatic fibrosis. She received a partial liver allograft (extended right lobe) from a deceased donor and developed recurrent fevers on day 2 after transplant without any infective source being evident. On postoperative day (POD) 5 she developed ascites and worsening abdominal pain, and blood tests revealed raised lactate, hypoglycemia, and eosinophilia (Fig. 1). There was additional evidence of graft dysfunction with elevations in alanine aminotransferase (ALT; 742 U/mL), bilirubin (335 μmol/L), and international normalized ratio (INR; 2.2), but no evidence of encephalopathy. An urgent liver biopsy demonstrated severe mixed T cell–mediated rejection (TCMR) and AMR with prominent eosinophils. In addition, foci of ischemic type necrosis and severe glycogen depletion of hepatocytes were present (Fig. 2). Complement component 4d (C4d) showed focal linear portal vein staining and HLA class 2 DSAs (DQ6, DQ7, and DR13), each with mean fluorescence intensities (MFIs) of >20,000 present in the patient's serum on POD 6. The patient did not respond to 2 courses of intravenous methylprednisolone (1 g); a repeat biopsy on POD 16 demonstrated strong C4d staining of the portal veins and microvasculature, and she was treated with plasma exchange. The patient was discharged on POD 31 and remains in good health 8 months after transplant.

The second case was a 48-year-old woman who received a transplant for primary biliary cirrhosis with a whole-liver allograft from a deceased donor. On POD 6 this patient developed a similar

Abbreviations: ABO-C, ABO compatible; ALT, alanine aminotransferase; AMR, antibody-mediated rejection; C4d, complement component 4d; DSA, donor-specific antibody; HLA, human leukocyte antigen; INR, international normalized ratio; MFI, mean fluorescence intensity; POD, postoperative day; TCMR, T cell–mediated rejection.

Address reprint requests to Desley A. H. Neil, B.Med.Sc., M.B.B.S., Ph.D., F.R.C.Path., Department of Cellular Pathology, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2GW, UK. Telephone: +44 121 371 3349; FAX: +44 121 371 3333; E-mail: Desley.neil@uhb.nhs.uk

**These authors are joint senior authors.*

James M. Halle-Smith participated in curating data and writing the original draft. Angus Hann participated in writing, reviewing, and editing. Owen L. Cain participated in curating data, writing, reviewing, and editing. M. Thamara P. R. Perera and Desley A. H. Neil participated in conceptualizing, writing, reviewing, and editing.

Received March 16, 2021; accepted May 6, 2021.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.26101

Potential conflict of interest: Nothing to report.

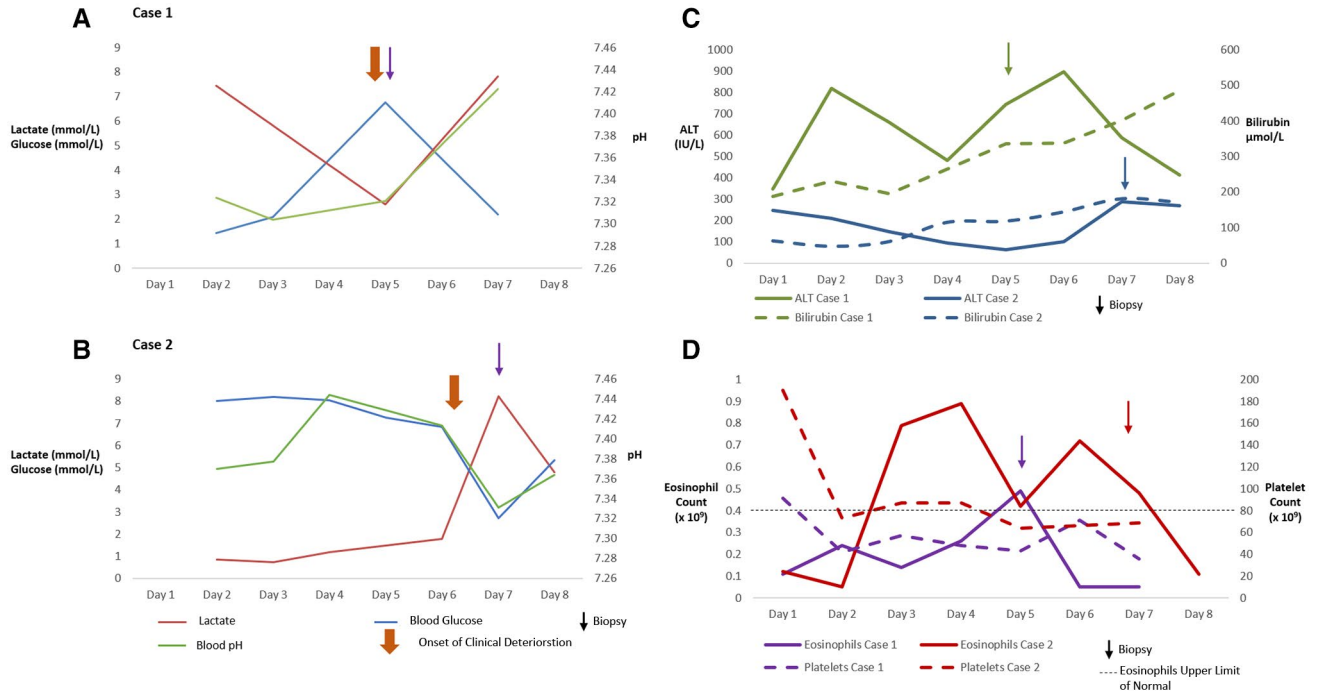

FIG. 1. Graph of postoperative blood results. (A) Graph demonstrates the lactate, blood glucose, and pH trend for the 23-year-old female patient and (B) the 48-year-old female patient during the initial postoperative period. (C) Postoperative ALT and bilirubin levels are shown for both cases as well as the (D) postoperative eosinophilia and thrombocytopenia in both cases (upper range of normal limit, 0.4×10^9).

clinical syndrome of hypoglycemia, lactic acidosis, and eosinophilia. There was a concomitant rise in ALT (289 IU/L), aspartate aminotransferase (160 IU/L), bilirubin (181 mmol/L), and INR (2.0), but no evidence of encephalopathy (Fig. 1). Severe mixed TCMR and AMR rejection with prominent eosinophils was demonstrated on biopsy in addition to foci of ischemic-type coagulative necrosis and severe glycogen depletion (Fig. 2). There was strong linear C4d staining of the poral vein and microvasculature, sinusoids, and hepatic veins and HLA class 2 DSAs (DQ6, DR15, and DR51), each with MFIs of >20,000 detected on POD 7. The patient's graft function improved following a course of intravenous methylprednisolone. At 1 month after transplantation, the patient was readmitted with ascites and a right pleural effusion. A repeat liver biopsy again demonstrated portal microvascular C4d staining. Additional features of persistent untreated AMR were also identified, and these included portal sclerosis, portal venopathy, and loose hepatic venoocclusive lesions as well as subtle features of venous outflow obstruction. There was no active TCMR component identified on this repeat biopsy.

Definitive evidence of AMR was demonstrated in both of these cases (portal microvasculitis, eosinophilic venulitis, positive C4d staining, and high-serum DSAs), coexisting with TCMR.[3] Because of the rapid onset following transplant, the AMR component was most likely caused by preformed DSAs. Both patients were at risk of prior sensitization having had previous blood transfusions and prior pregnancies.[4] Identifying sensitized recipients at risk of early AMR through DSA measurements while awaiting transplant may be beneficial. In addition to the histological features previously described in AMR,[3] both patients had prominent eosinophils in their biopsies, and these have previously been found to correlate with DSAs.[5] Thrombocytopenia was present in both cases from the time of transplant with no clear association with the rejection episode. An interesting pattern of ischemic-type necrosis and hepatocellular glycogen depletion was evident; neither of these features are typically seen in TCMR and to our knowledge have not previously been described in AMR. Early loss of liver grafts labeled as 'massive hemorrhagic necrosis' of hepatocytes, describes progressive coagulative necrosis similar to what we have described. However the distribution of necrosis in this situation is different to our

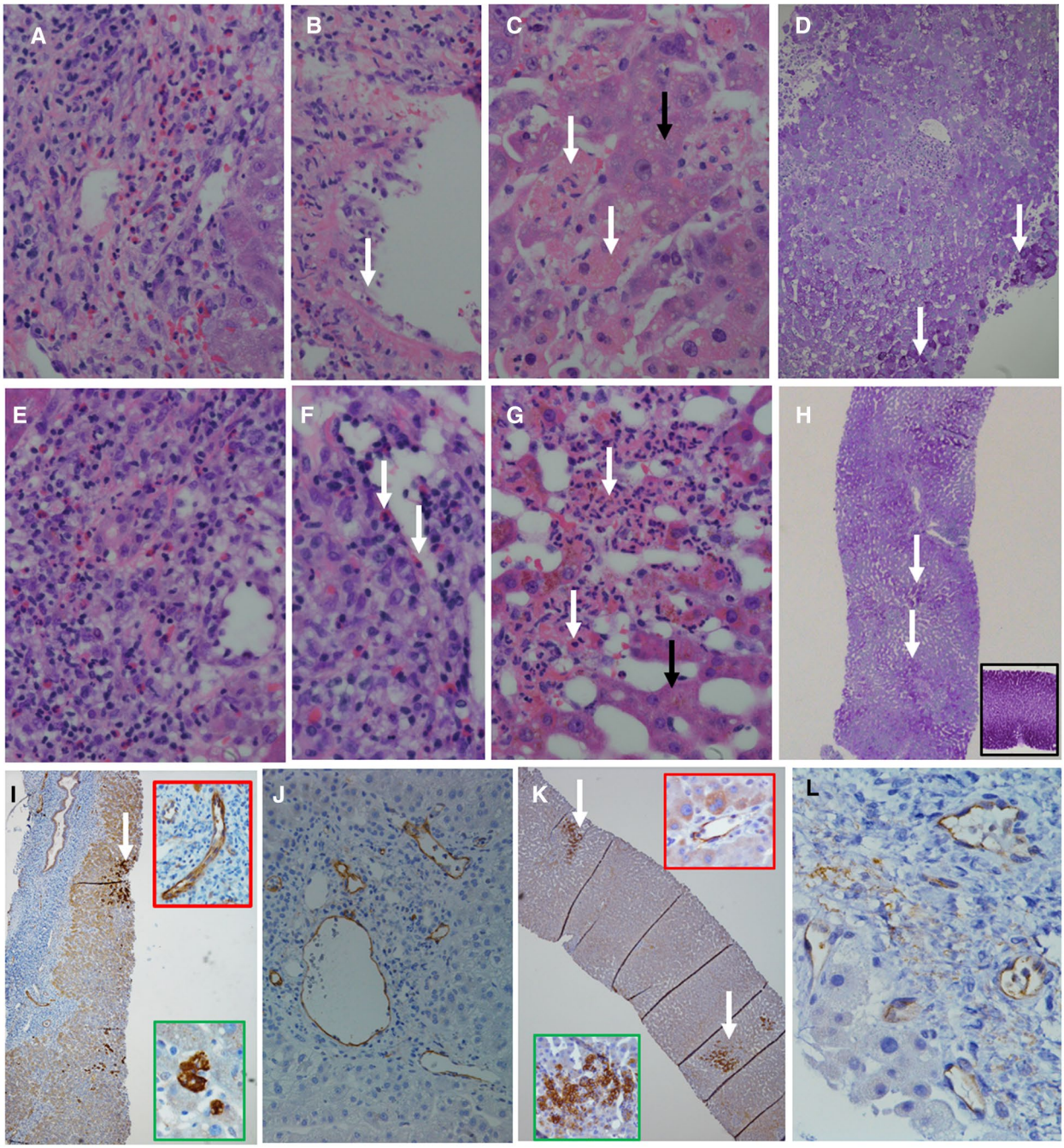

FIG. 2. Histological evidence of AMR. The histological evidence of AMR in both cases is demonstrated. (A-D) Case 1. (E-H) Case 2. (A and E) Prominent eosinophils (red) in portal infiltrate. (B and F) Eosinophilic venulitis. Arrows point to eosinophils in veins. (C and G) Foci of ischemic necrosis with neutrophil infiltrate. White arrows point to pale pink necrotic hepatocytes. Black arrows point to viable purplish hepatocytes. (D and H) Periodic acid–Schiff stain demonstrating the glycogen depletion (pale staining) of most hepatocytes with a few glycogen-containing hepatocytes (arrows) staining a darker purple. Insert showing normal glycogen content (dark purple staining) in a posttransplant biopsy for comparison. (I-L) C4d immunohistochemistry: (I and J) case 1; (K and L) case 2. (I and K) Distribution of ischemic necrosis seen with C4d staining (brown) of the necrotic hepatocytes (arrows) at the time of the first biopsy. Green-outlined insets are a higher power of the necrotic hepatocytes staining with C4d. Red-outlined insets are a higher power of the brown linear C4d vessel staining. (J and L) Persistent positive (brown linear) vascular C4d staining in portal tracts in the subsequent biopsy at day 16 and 1 month after transplant, respectively.

2 cases, which have an apparently random distribution and are not associated with hemorrhage.[6] Our hypothesis is that liver ischemia occurred as a result of AMR vasculitis and an associated intrahepatic thromboembolic phenomenon. Portal venulitis also contributed to the ischemic injury. This process accounted for the early clinical manifestations of hypoglycemia and raised lactate and liver enzymes. Severe acute AMR should be considered in liver transplant recipients who develop graft dysfunction with associated eosinophilia, hypoglycemia, and lactic acidosis as these are evident before DSA results are available. As thrombocytopenia is common in the early post–liver transplant setting, a drop in platelets may not be a useful marker of an AMR-related thrombotic microangiopathy; however, more detailed assessment of the time to recovery of normal platelet numbers may be useful. We propose that glycogen depletion and foci of ischemic hepatocyte necrosis be considered features of severe AMR.

James M. Halle-Smith, B.Med.Sci., M.B.Ch.B.[1]
Angus Hann, B.Sc., M.B.B.S. (Hons), M.R.C.S.[1,2]
Owen L. Cain, B.Med.Sc., M.B.Ch.B. (Hons), F.R.C.Path.[3]
M. Thamara P. R. Perera, M.B.B.S., M.S., F.E.B.S., M.D., F.R.C.S.[1*]
Desley A. H. Neil, B.Med.Sc., M.B.B.S., Ph.D., F.R.C.Path.[2,3*]

[1]Liver Unit
Queen Elizabeth Hospital Birmingham
Birmingham, United Kingdom
[2]Institute of Immunology and Immunotherapy
University of Birmingham
Birmingham, United Kingdom
[3]Department of Cellular Pathology
Queen Elizabeth Hospital Birmingham
Birmingham, United Kingdom

REFERENCES

1) Demetris AJ, Zeevi A, O'Leary JG. ABO-compatible liver allograft antibody-mediated rejection: an update. Curr Opin Organ Transplant 2015;20:314-324.
2) O'Leary JG, Kaneku H, Demetris AJ, Marr JD, Shiller SM, Susskind BM, et al. Antibody-mediated rejection as a contributor to previously unexplained early liver allograft loss. Liver Transpl 2014;20:218-227.
3) Demetris AJ, Bellamy C, Hübscher SG, O'Leary J, Randhawa PS, Feng S, et al. 2016 comprehensive update of the Banff Working Group on liver allograft pathology: introduction of antibody-mediated rejection. Am J Transplant 2016;16:2816-2835.
4) Vionnet J, Sempoux C, Pascual M, Sánchez-Fueyo A, Colmenero J. Donor-specific antibodies in liver transplantation. Gastroenterol Hepatol 2020;43:34-45.
5) O'Leary JG, Michelle Shiller S, Bellamy C, Nalesnik MA, Kaneku H, Jennings LW, et al. Acute liver allograft antibody-mediated rejection: an inter-institutional study of significant histopathological features. Liver Transpl 2014;20:1244-1255.
6) Hübscher SG, Adams DH, Buckels JA, McMaster P, Neuberger J, Elias E. Massive haemorrhagic necrosis of the liver after liver transplantation. J Clin Pathol 1989;42:360-370.